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A Comprehensive Review of Molecular Mechanisms Involved in Development of Porphyria, Due to Defective Porphyrin Biosynthesis in the Human Body

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Abstract

Porphyrins are cyclic organic molecules comprised of four pyrrole rings, linked by a methine bridge, consisting of the double bond of carbon atoms, which form a chelation compound with a metal ion like magnesium, cobalt, iron, or nickel in the center. Porphyrins form the basis for many biologically important haem proteins like hemoglobin and myoglobin, cytochromes, cobalamine (vitamin B12) in animals, and chlorophyll in plants. Defects in the endogenous synthesis of porphyrin rings in humans lead to a medical condition called porphyria. These are characterized by congenital enzyme defects in molecular pathways leading to the accumulation of intermediate porphyrin products that exhibit cellular and metabolic toxicity in a myriad of ways. Enzyme blocks can also be acquired later in life, like for example lead poisoning. This chapter explores the manifestation of the various clinical features based on molecular mechanisms.

***Keywords*:** Porphyrins, porphyrias, porphyrin synthesis, congenital enzyme defects, metal chelation

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Umar Ali Dar, Mohd. Shahnawaz and Puja Gupta (eds.) Porphyrin-Based Composites: Materials and Applications, (259–272) © 2025 Scrivener Publishing LLC

10.1 Porphyrin Composites in Medicine – An Introduction

Hans Fischer was the first to elucidate the structure of several natural porphyrins. Shemin and Rittenberg using radiolabeled molecular probes, discovered that the nitrogen atom in porphyrin protoporphyrin IX was derived from amino acid glycine. Porphyrin composites are materials that contain porphyrins, which are a class of pigments that occur naturally in many organisms, including plants and animals. Porphyrins are characterized by a ring-like structure that contains nitrogen atoms and can bind to metal ions. Porphyrin composites are typically made by combining porphyrins with other materials, such as metals, polymers, or semiconductors, to create new materials with unique properties. Numerous practical applications of these molecules have been studied, comprising of imaging, energy applications, and sensing.

10.2 Nature of Porphyrins

Porphyrins are a class of pigments that are ubiquitous and are found in many organisms belonging to diverse kingdoms like plants, algae, and animals. Porphyrins in the form of tetrapyrrole ring molecules are found in all living organisms. They are characterized by a ring-like structure that contains four pyrrole units and can bind to metal ions such as iron or magnesium, forming metallo-porphyrins. Pyrroles are heterocyclic aromatic compounds that serve as crucial structural building blocks for a variety of bioactive substances like chlorophyll (plants) and heme (animals). Heme, the molecule responsible for the red color of blood, is a well-known example of metalloporphyrin.

Porphyrins, due to their ability to bind with other molecules and form complex structures, are of great interest to a biochemist. Porphyrins and their derivatives are also used in medicine as a diagnostic tool and as a therapeutic agent.

10.3 Porphyrin Biosynthesis in Humans

The biosynthesis of porphyrins begins with the amino acid glycine, which is a key precursor of the pathway. The porphyrin nucleus synthesis is the backbone of heme proteins like hemoglobin and cytochromes. Heme controls

the manufacture of porphyrin in higher eukaryotes by acting as a feedback inhibitor of the pathway's initial steps. The sequence of enzymes involved in the heme biosynthesis of humans is depicted in the Figure 10.1.

Glycine is transported into the mitochondria by the glycine transporter (refer to Figure 10.1) by erythroid-specific mitochondrial carrier protein SLC25A38. Then, in the mitochondrial phase, succinylCoA and glycine react in higher eukaryotes to produce alpha amino beta ketoadipic acid. It is then converted to 5-aminolevulinate by decarboxylation. 5-aminolevulinate dehydratase catalyzes the formation of the pyrrole moiety by causing the condensation of two 5-aminolevulinate molecules to produce porphobilinogen.

In another pathway operational in plants, algae, and most microorganisms, amino acid glutamate is the precursor and not glycine, and glutamate is directly converted to 5-aminolevulinate. First, glutamate is esterified to produce glutamyl-tRNA. The tRNA is cut from glutamate 1-semialdehyde, which is produced when glutamate is reduced by NADPH. The glutamate 1-semialdehyde is changed into 5-aminolevulinate by an aminotransferase and the rest of the pathway is the same.

In all living things, two molecules of 5-aminolevulinate condense to produce porphobilinogen, and four molecules of porphobilinogen combine to form protoporphyrin through a series of intricate enzyme processes.

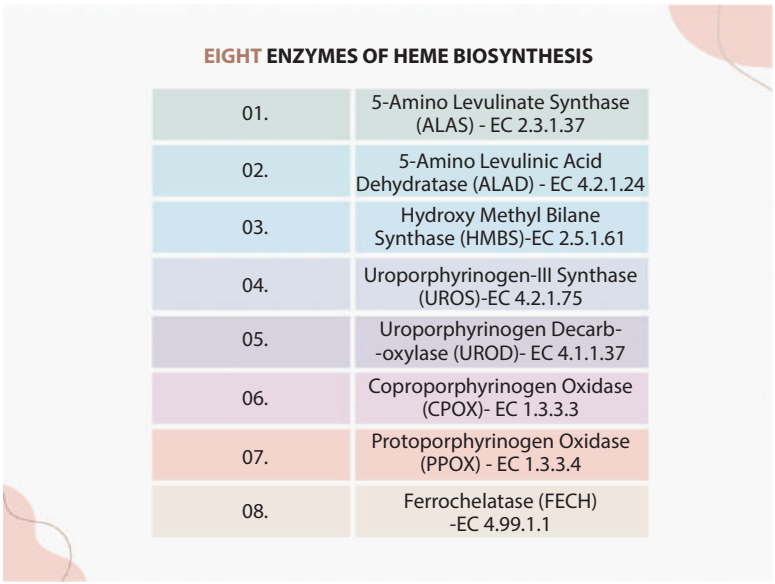

Figure 10.1 Eight enzymes involved in biosynthesis of haem, first and last 3 are found in mitochondria rest are localized in cytoplasm of all cells. Our original illustration.

After the protoporphyrin has been put together, the iron atom is added in a process that is aided by the enzyme ferrochelatase.

Heme is a porphyrin-coordinated coordination compound of Fe2+ comprised of a 4.14; protoporphyrin IX ring. Hemes are elements of hemoglobin, the red blood cell pigment. Chlorophyll, the green pigment found in plants, is another example. A central magnesium is chelated to a porphyrin unit. Light is absorbed by chlorophyll and transformed into chemical energy for photosynthesis in plants. One form, chlorophyll a, has a structure that is displayed. The chemical reaction that occurs during photosynthesis is the transformation of carbon dioxide and water into carbohydrates and oxygen.

10.4 Porphyria- Erythropoietic Disorders Due to Defects in Porphyrin Metabolism

Greek "Porphyria," which means "purple," is where the term porphyrin gets its etymology. As shown in Figure 10.1 eight distinct enzymes are involved in the endogenous production of porphyrin rings, starting with the basic amino acids' glycine and succinic acid. Cytosolic enzymes make up four of them, while mitochondrial enzymes make up the first and last three. Tricarboxylic acid (TCA) cycle and an oxygen source are required for synthesis. Sometimes the defects affect both tissues equally. Alcohol, stress, infections, malnutrition, hormonal changes (like menstruation), certain medicines, and stress can all trigger porphyrias in genetically predisposed individuals. Since these medications are inducers of cytochrome P-450 and decrease the amount of free heme in the mitochondria, they are likely to hasten acute symptoms in sensitive individuals.

Figure 10.2 illustrates several human disorders collectively referred to as porphyrias are brought on by genetic abnormalities in the manufacture of porphyrins, which can result in the accumulation of pathway intermediates. These are inherited biochemical diseases that disrupt the metabolism of heme, which is a component of the protein hemoglobin, tasked with the function of oxygen transport in the erythrocytes. Heme is synthesized from a precursor molecule called porphyrin, and the different types of porphyria are caused by gene impairments in the enzymes that are responsible for heme-synthesis. Symptoms may include skin sensitivity to sunlight, which can lead to blistering and scarring, as well as nervous system symptoms such as abdominal pain, seizures, and mental changes.

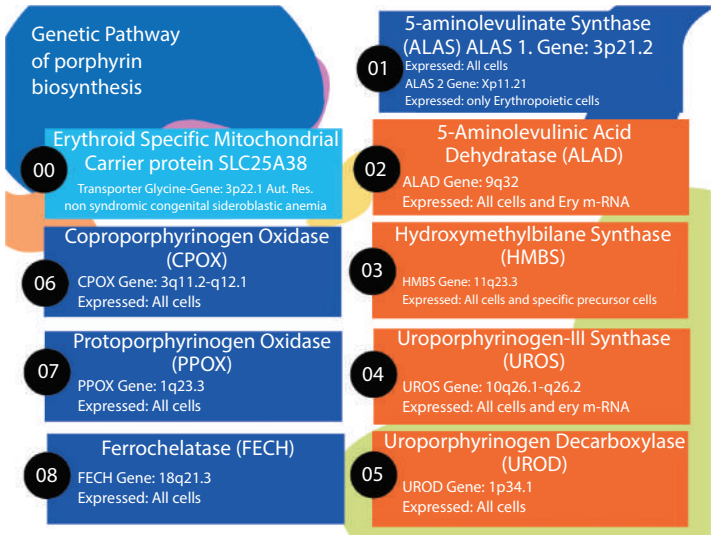

Figure 10.2 Genetic pathway of porphyrin synthesis in human beings. Defective gene leads to porphyrias. Our original illustration.

Inherited, genetic porphyrias are generally rare but acquired disorders are more common, like porphyria cutanea tarda, which can be caused by environmental factors such as alcohol consumption and exposure to certain chemicals. The treatment is variable and is in accordance with the type and severity of the porphyria, and may include measures to manage symptoms, such as pain relief, and avoiding triggers that can worsen symptoms, such as alcohol. In some cases, medications or heme therapy may also be used. In other cases, liver transplantation may be curative as healthy hepatocytes produce the absent enzymes.

Porphyrias are classified into two main groups: Acute porphyrias, Hepatic porphyrias, and Cutaneous porphyrias. They are subclassified into various groups based on the nature of the deranged enzyme.

10.4.1 Acute Porphyrias

Acute porphyrias, such as acute intermittent porphyria and hereditary coproporphyria, primarily impact the nervous system and may lead to symptoms including abdominal pain, muscle weakness, seizures, and psychiatric disturbances. These conditions include acute intermittent porphyria (most common), variegate porphyria, hereditary coproporphyria, and 5-Aminolevulinate dehydratase enzyme deficiency porphyria.

A study published in 2022 investigated the prevalence and clinical features of acute porphyrias in a cohort of patients in the Netherlands. The researchers found that the prevalence of acute intermittent porphyria mutations was approximately 1 in 1,700 individuals, while the clinical penetrance was estimated to be at 1–2%. The study also highlighted that the clinical penetrance was higher in first-degree relatives of known patients, at around 20%.

10.4.1.1 Hepatic Porphyrias

These are hepatic porphyrias that lead to liver and biliary diseases on account of excessive accumulation of protoporphyrin. These include X-linked protoporphyria and erythropoietic protoporphyria. Hepatocellular carcinoma (live cancer) is a risk for both these conditions variegate, and acute intermittent porphyrias.

10.4.2 Cutaneous Porphyrias

Cutaneous porphyrias, which include porphyria cutanea tarda and congenital erythropoietic protoporphyria. These primarily affect the skin and can cause symptoms such as sensitivity to sunlight, light-induced vesicles (aka Photosenstive rash, clinical photographs Figure 10.3), blisters, erosions of skin, skin fragility, and scarring.

There are several different types of cutaneous porphyria, each caused by mutations in different genes. The symptoms of cutaneous porphyria are variable among the affected individuals and even among family members

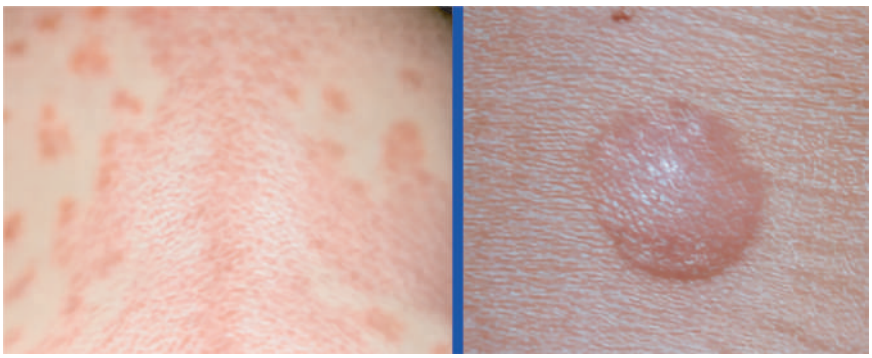

Figure 10.3 Photosensitive rash of a patient that developed after exposure to sunlight and close-up of a cutaneous blister, both these features are highlights of skin lesions in Porphyrias. Our original photograph.

with the same type of genetic mutation. Porphyria cutanea tarda can triggered by iron overload, alcohol, estrogens, and renal failure.

Treatment options depend on the specific type of cutaneous porphyria and may include avoiding triggers, such as sun exposure, and taking medications to reduce symptoms.

10.4.2.1 Acute Intermittent Porphyria (AIP)

The most prevalent type of porphyria is the Acute intermittent variant, which is caused by a deficit of the biochemical enzyme, hydroxymethylbilane synthase (abbreviated as HMBS) Porphobilinogen deaminase (abbreviated PBGD) is a synonym for this protein. This enzyme is responsible for the production of porphobilinogen (PBG), a precursor to heme. Mutation of the enzyme gene leads to the synthesis of an anomalous enzyme protein that has decreased action and consequent increase in the concentration of porphobilinogen in the body. This build-up of porphobilinogen causes the main symptoms of AIP, which can include pain in the abdomen, convulsions, queasiness, weakness in the muscles, and psychological and behavioral disturbances.

AIP is inherited in an autosomal dominant pattern, meaning that an individual only needs to inherit one copy of the defective gene to develop the condition. This rare disorder is estimated to affect 1 in 75,000 to 200,000 people worldwide. The exact mechanism by which elevated levels of PBG and ALA lead to symptomatic disease remains unclear, as most individuals with the genetic defect do not exhibit symptoms despite increased porphyrin secretion.

Recent studies have suggested an association between AIP and systemic inflammation, highlighting the potential role of inflammatory processes in the pathogenesis of AIP. Additionally, there are reports of higher prevalence of AIP in specific ethnic groups, such as Argentina and Spain, due to the founder effect. Acute intermittent porphyria is a low-penetrant genetic metabolic disease, with penetrance estimated to be around 10% to 20%. However, higher penetrance has been linked to specific mutations, while the overall genetic susceptibility factors underlying penetrance remain unknown.

Treatment of AIP involves managing symptoms and avoiding triggers such as alcohol and certain medications. Heme therapy, which replaces the missing enzyme, is also used to prevent attacks and manage symptoms. Preventive measures like avoiding the triggers that can cause an attack, and having a healthy diet and lifestyle are important for people with AIP.

10.4.2.2 Hereditary Coproporphyria (HCP)

Hereditary Coproporphyria (HCP) is another type of acute porphyria characterized by a deficiency in the enzyme coproporphyrinogen III oxidase (CPOX). This enzyme plays a crucial role in the production of coproporphyrinogen III, a precursor to heme. A genetic mutation in the CPOX gene results in the formation of an abnormal enzyme with reduced activity, leading to an accumulation of coproporphyrinogen III in the body. This build-up of coproporphyrinogen III contributes to the symptoms of HCP, which can include abdominal pain, muscle weakness, seizures, and psychiatric disturbances.

HCP is inherited in an autosomal dominant pattern, meaning that an individual only needs to inherit one copy of the defective gene to develop the condition. This rare disorder affects an estimated 1 in 100,000 to 200,000 people worldwide. In some cases, the disorder may cause life-threatening complications if not properly diagnosed and treated.

Recent research has highlighted the potential role of inflammation in the pathogenesis of HCP. Additionally, there are reports of higher prevalence of HCP in certain ethnic groups, such as Argentina and Spain, due to the founder effect. Furthermore, HCP is a low-penetrant genetic metabolic disease, with penetrance estimated to be around 10% to 20%. However, higher penetrance has been linked to specific mutations, while the overall genetic susceptibility factors underlying penetrance remain unknown.

Compared to Acute Intermittent Porphyria (AIP), HCP has a lower prevalence and is characterized by a deficiency in a different enzyme (CPOX) involved in the heme synthesis pathway. While both disorders share some common symptoms, such as abdominal pain, muscle weakness, seizures, and psychiatric disturbances, the specific enzyme deficiency and the accumulation of different precursors (coproporphyrinogen III in HCP and porphobilinogen in AIP) set these two disorders apart.

10.4.2.3 Congenital Erythropoietic Porphyria (CEP)

Congenital Erythropoietic Porphyria (CEP), also referred to as Günther's disease, is a rare autosomal recessive disorder that impacts the heme biosynthesis process, leading to an insufficiency of the uroporphyrinogen III synthase enzyme. The scarcity of this enzyme results in the buildup of porphyrins, primarily in developing red blood cell precursors, causing an array of complications. The hallmark feature of CEP is extreme sensitivity to sunlight, where even brief exposures lead to painful blisters and potential scarring. Additional symptoms might encompass anemia, jaundice,

and abdominal discomfort. As a recessive condition, affected individuals inherit two faulty gene copies, one from each parent. Management strategies typically focus on mitigating sunlight exposure, along with possible interventions like blood transfusions or bone marrow transplantation under specific circumstances. To date, approximately 220 instances of CEP have been documented worldwide since its initial characterization in the late nineteenth century. Researchers attribute the causative factor to mutations in the UROS gene (OMIM #263700), which codes for the uroporphyrinogen III synthase involved in the heme biosynthetic pathway. These mutations hinder proper enzyme function, subsequently triggering porphyrin accumulations in the bone marrow, circulating erythrocytes, plasma, urine, teeth, and bones in fetuses. Such accumulations instigate cutaneous photosensitivity and hemolytic anemia in more critical situations.

10.4.2.4 Porphyria Cutanea Tarda (PCT)

Porphyria Cutanea Tarda (PCT) refers to a group of acquired and familial disorders linked to decreased activity of the heme synthetic enzyme uroporphyrinogen decarboxylase (UROD), resulting in skin issues such as fragility, blistering, and hyperpigmentation upon sunlight exposure. While PCT is predominantly acquired, about 10-20% of cases exhibit genetic factors. Common triggers include excessive alcohol intake, estrogen use, HIV, hepatitis C, and hemochromatosis – an iron overload disorder. Partial oxidation of uroporphyrinogen to uroporphomethene, an UROD inhibitor, plays a significant role in PCT pathogenesis.

Treatment of PCT may include avoiding triggers, such as sun exposure, and taking medications to reduce symptoms. A medication called hydroxychloroquine is often used to reduce the activity of UROD and decrease the production of porphyrins. In addition, Phlebotomy to decrease iron in the liver is also recommended. If the underlying cause, such as hepatitis C or heavy alcohol consumption, can be identified and treated, this may also help to reduce symptoms of PCT.

Recent research highlights the impact of HFE gene mutations in PCT progression, particularly in conjunction with hemochromatosis and hepatitis C. Treatments involve managing underlying conditions, reducing triggers, and utilizing phlebotomy or low-dose hydroxychloroquine to enhance UROD activity and decrease porphyrin levels. Regular monitoring of liver functions, iron status, and porphyrin levels ensures effective management and early detection of any recurrence or complications. Additionally,

advances in understanding the molecular mechanisms behind PCT have opened new avenues for targeted therapeutic approaches.

10.4.2.5 Variegate Porphyria (VP)

A rare hereditary condition called variegate porphyria (VP) interferes with the metabolism of heme, a substance found in hemoglobin. Porphyrins build up in the body because of a protoporphyrinogen oxidase (PPOX) enzyme deficiency, which is what causes it. Because VP is inherited in an autosomal dominant manner. An affected individual has a probability of p=0.5 or a 50% probability of passing this disorder on to each of his or her progenies. Skin sensitivity to sunlight, stomach pain, neurological problems, and a higher risk of liver damage are some of the signs and symptoms of VP. Aside from avoiding sunlight, treatment options include medications like hemin, oral chloroquine, and beta-carotene. Although there is presently no treatment for VP, early detection and intervention can help to avoid or lessen symptoms.

10.4.2.6 Erythropoietic Protoporphyria (EPP)

An uncommon genetic condition called erythropoietic protoporphyria (EPP) interferes with the metabolism of heme, a substance found in hemoglobin. A lack of the biological enzyme ferrochelatase causes unused protoporphyrin molecules to accumulate in the body. Protoporphyrin is noxious to cells and manifests as extreme photosensitivity, which is characterized by an excessive sensitivity to sunlight, as well as pain, itchiness, and redness of the skin (akin to the famous, fictional character created by Irish author Bram Stoker, vampire Dracula). Treatment options for the disorder, which is inherited in an autosomal recessive way, include beta-carotene, Afamelanotide, and oral chloroquine. While there is no known treatment for EPP, symptoms can be reduced by avoiding sunlight.

10.5 Acquired Porphyrias Due to EXCESsive Arsenic and Lead Exposure

Many of the toxic elements and heavy metals are known to interfere with several enzymes related to the heme biosynthetic pathway and are known to present like porphyrias. Groundwater contamination by the leather tanning industry leads to arsenic and mercury exposure in many parts

of India. Heavy metals can lead to altered coproporphyrin touroporphyrin and coproporphyrin I to coproporphyrin III ratios. Lead is a known inhibitor of PBG synthetase (porphobilinogen synthetase enzyme), ferrochelatase, delta-amino Levulinic acid dehydratase (ALAD), and coproporphyrinogen oxidase. This leads to the accumulation of 5-aminolevulinic acid and erythrocyte protoporphyrin IX, which is a useful marker to lead toxicity. Excessive lead exposure, at the onset, may lead to elevated erythrocyte protoporphyrin XI to levels greater than 60 mg/dL. Delta-amino Levulinic acid dehydratase ALAD elevation indicates medium to high levels of exposure to lead. Serum lead (pb) levels may normalize within a short period of time after exposure hence this direct analysis is of little clinical utility.

10.6 Diagnosis of Porphyrias

A thorough medical history reveals unpleasant episodes such as abdominal discomfort, prodrome, aggravating, and reliving variables, such as alcohol consumption, skin lesions, and most frequently weakness brought on by neurological symptoms. Along with past use of alcohol and tobacco, all current and previous drugs should be carefully reviewed for any possible

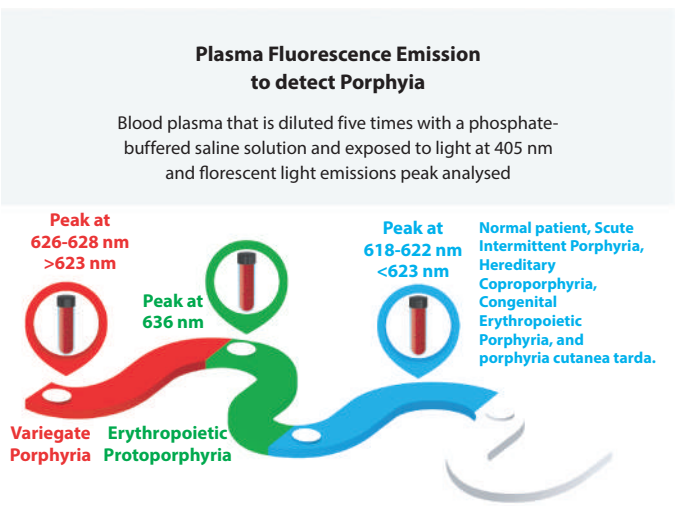
Plasma Fluorescence Emission
to detect Porphyia
Blood plasma that is diluted five times with a phosphate-buffered saline solution and exposed to light at 405 nm and florescent light emissions peak analysed
Peak at
626-628 nm
>623 nm
Peak at
636 nm
Peak at
618-622 nm
<623 nm
Normal patient, Scute Intermittent Porphyria, Hereditary Coproporphyria, Congenital Erythropoietic Porphyria, and porphyria cutanea tarda.
Variegate Porphyria
Erythropoietic Protoporphyria

Figure 10.4 Plasma fluorescence technology to detect porphyrias. Our original illustration.

links to attacks. Oral contraceptive pills OCP and several other types of anticonvulsant medications are among the more frequent attack triggers.

High-performance liquid chromatographic (HPLC) analysis of blood, urine, and stool samples demonstrates elevated 5-aminolevulinate and porphobilinogen in AIP. These precursors may be elevated for weeks following an attack of AIP. As the level of hydration of the patient affects the urine concentration of porphobilinogen, this should be calculated as the ratio of porphobilinogen concentration to urine creatinine concentration. A normal porphobilinogen raises suspicion of lead poisoning as the cause of elevated 5-aminolevulinic acid in urine.

Plasma fluorescence screening scheme to screen for porphyria as depicted in the following path diagram (Figure 10.4) of the authors.

10.7 Newer Therapeutics for Porphyrias: Givosiran Treatment and Afamelanotide Application

Recent advancements in the treatment of porphyrias include Givosiran and Afamelanotide. Givosiran, a subcutaneously administered RNA interference (RNAi) therapeutic targeting ALAS1, has been approved for the treatment of acute hepatic porphyrias. Clinical trials demonstrated that monthly administration of Givosiran significantly reduced ALAS1 induction, leading to substantial decreases in ALA and PBG levels, and a reduction in attack rates by approximately 75%.

Afamelanotide, which is a long-acting analog of posterior pituitary melanocyte-stimulating hormone (MSH), has been found to be effective in treating patients with EPP. A Phase 3 trial of Afamelanotide improved the quality of life and sun exposure time tolerance of patients with EPP. The medication was well-tolerated and exhibited good clinical effectiveness in an 8-year observational study. Afamelanotide received FDA approval in 2014 and EMA European Medicines Agency approval in 2019.

10.8 Conclusion

Porphyrias are metabolic defects in the biosynthesis of Haem, which is a precursor of hemoglobin. These congenital enzymatic defects can present in a myriad of ways, ranging from neurological, gastrointestinal, hepatic, and cutaneous manifestations. Fecal, urine, and blood levels of porphyrin and their precursors are the main basis for establishing the clinical

diagnosis of porphyria. Each defect leads to decreased activity of a particular enzyme and accumulation of its precursor molecules due to blockade in the heme biosynthetic pathway. These precursors become elevated in the blood of the patient or get excreted in feces and urine or which are detected and used in establishing the diagnosis of porphyrias. Some heavy metal exposure like mercury, arsenic, and lead can also present like porphyrias.

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